IJPSR (2023), Volume 14, Issue 9 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 10 January 2023; received in revised form, 28 March 2023; accepted, 25 April 2023; published 01 September 2023

ANTIBIOTIC DE-ESCALATION IN BACTEREMIC UTI & ITS IMPACT ON COST AND LENGTH OF STAY-A PROSPECTIVE OBSERVATIONAL STUDY IN A TERTIARY CARE TEACHING HOSPITAL IN SOUTH KERALA

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Keywords:

Urinary tract infection, Antibiotic utilization pattern, De-escalation, Cost and length of stay

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ABSTRACT: Urinary tract infection (UTI) is one of the most common infections affecting humans and is one of the leading causes of both community-acquired and nosocomial infections. The study's objective was to assess the rate of de-escalation and the impact of de-escalation on cost and length of stay, antibiotics utilization pattern, and adverse effects of antibiotics in bacteremic UTI. A prospective observational study was conducted on 218 UTI patients in a tertiary care hospital in Trivandrum for 6 months. The results showed that the incidence of UTI is higher in females. The most common symptom was identified as fever, followed by dysuria. Escherichia Coli was the causative organism in most of cases. Inj. Cefoperazone and Sulbactum was the most frequently prescribed antibiotic. Gastric irritation was experienced by 1.8% of patients followed by exanthema in 0.5% patients. The rate of successful de-escalation was 26.9% while 73.1% failed de-escalation. A significant association (p-value < 0.001) was found between de-escalation failure and length of stay. According to our study, the absence of de-escalation increased the cost of antibiotics prescribed. 36.1% of patients had a difference in cost per day between 0-100 rupees, followed by 30.1% in a 100-500 rupees range. A significant association (p-value < 0.001) between de-escalation failure and cost was noted. This study proves that de-escalation was associated with better patient outcomes, *i.e.*, reduced hospital length of stay. The study shows a perspective for bettering the current de-escalation rate.

INTRODUCTION: Urinary tract infection (UTI) is one of the most common infections affecting humans and is one of the leading causes of both community-acquired and nosocomial infections. It is an inflammatory disorder of the urinary tract caused by the abnormal growth of pathogens [1, 2].

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DOI: 10.13040/IJPSR.0975-8232.14(9).4572-79

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.14(9).4572-79

The most common causative of UTI is gram-negative microorganisms such as Enterobacteriaceae; most monomicrobial UTIs are caused by Escherichia coli [3].

UTIs such as cystitis (lower UTIs) and pyelonephritis (upper UTIs) in healthy hosts with no history of UTIs are recognized as uncomplicated UTIs. In contrast, complicated UTIs are normally seen in the elderly and catheterized patients [4]. De-escalating antibiotics is a component of an antibiotic stewardship strategy that aims to treat infections effectively without using broad-spectrum

antibiotics for an extended period [5]. Antibiotic de-escalation should not be considered a reason to continue antibiotics in the absence of an infection. There is a belief that narrow spectrum antibiotics are harmless and can continue for longer periods. On the one hand, narrower agents will still cause AMR to emerge; conversely, continuing antimicrobials in the absence of infection may reduce the quality of diagnostic decision-making. Finally, the pharmacokinetics of broad and narrow-spectrum antimicrobials may differ, resulting in insufficient efficacy [6]. International guidelines recommend broad-spectrum antibiotics to minimize the risk of inadequate antimicrobial treatment, which has been shown to increase mortality [7].

Antibiotic resistance is defined as the bacteria not inhibited by an antibiotic's usually achievable systemic concentration with a normal dosage schedule and or falling in the minimum inhibitory concentration (MIC) range. Likewise, multiple drug resistance is the resistance to two or more drugs or drug classes. It occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals or other agents designed to cure or prevent the infection. In India, like several other developing countries, irrational use of antibiotics results from the widespread availability of these drugs, causing inappropriate use and ultimately resulting in steady increase in antibiotic resistance.

Irrational use of antibiotics not only increases the resistance but also reduces the quality of drug therapy, leading to increased morbidity and mortality, waste of resources heading to reduced availability of other vital drugs, increased cost, increased risk of unwanted effects such as drug interaction, adverse drug reaction and impact on psychosocial behavior of patients that there is ‘a pill for everything ill’ which may cause an apparent increased demand for drugs [8]. This study was aimed at studying the antibiotic utilization pattern and checking whether the drugs are properly de-escalated by the protocol formulated by the “Consortium for Infectious Disease Control” by the physicians in Kerala.

MATERIALS AND METHODS: A prospective observational study was conducted on UTI patients in a tertiary care hospital in Trivandrum using a convenience sampling technique for 6 months. The sample size for the study was 218 and it was calculated using the following formula:

$$\text{Sample size } n = N \times [Z^2 \times p \times (1-p)/e^2] / [N - 1 + (Z^2 \times p \times (1-p)/e^2]$$

Where N = Population size (425), Z = Critical value of the normal distribution at the required confidence level (2.58), p = Sample proportion (0.5), e = Margin of error (0.05)

Inclusion Criteria and Exclusion Criteria: All the inpatients with urinary tract infections above 18 years and urine culture positive, regardless of sex, were enrolled. Excluded patients include those receiving antibiotics, psychiatric patients, pediatric patients aged 0-18 years, and those with any other site infection.

Study Period: 2019 October to 2020 March

Study site: Tertiary care hospital, Neyyattinkara, Thiruvananthapuram, Kerala, India.

Study Procedure: A specially designed proforma was prepared to collect data which included patient demographics, laboratory data, drug details (name of the drug, dosage form, frequency, route of administration, duration of treatment, and hospital stay), and urine culture report were noted from the case record. The different brands of commonly used antibiotic drugs were sorted out by referring the hospital pharmacy and the pharmacist. The prescribing and dispensing details of antibiotics from each prescription were recorded in data acquisition form. In situations where the physician de-escalated the antibiotic after obtaining the culture report, it was analyzed and assessed by the protocol formulated by the “Consortium for Infectious Diseases Control” by the physicians in Kerala.

Statistical Analysis: The data were entered and summarized in a Microsoft Excel worksheet, and routine descriptive statistics were applied using SPSS version 22. Categorical data were analyzed by chi-square test. All data were expressed as percentages for categorical variables.

Ethical Consideration: Written informed consent, necessary permission, and clearance for the study were obtained from the Institutional Ethics

Committee (IEC) with an IEC approval number NIMS/IEC/2019/01.

RESULTS:

Demographic Characterization: Participants in the study were divided into 6 groups according to their age. Among 218 patients diagnosed with UTI, it was found that the highest number of study subjects belonged to the age group of 46-55 years (24.1%) of which 41 (19.0%) were females.

The infection rate is high in postmenopausal women because of bladder or uterine prolapse, causing incomplete bladder emptying, loss of estrogen with attendant changes in vaginal flora, which allows peri-urethral colonization with gram-negative aerobes such as Escherichia coli (*E. coli*). The prevalence of UTI in elderly men and women was similar and 36% of it was catheter-associated **Fig. 1.**

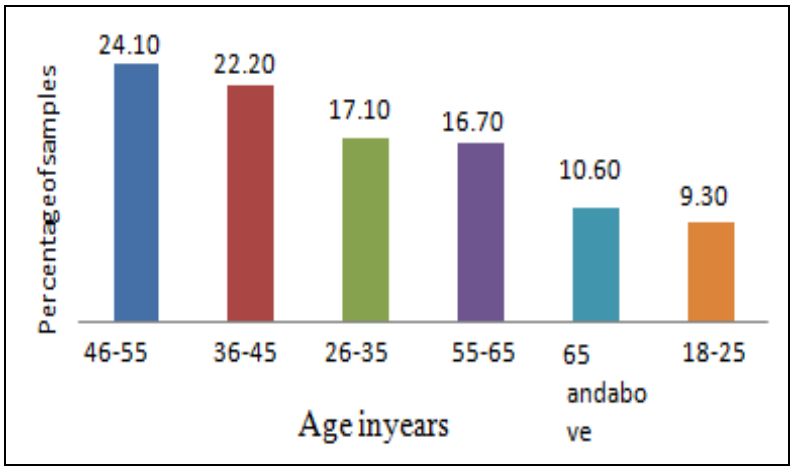

FIG. 1: PERCENTAGE DISTRIBUTION OF SAMPLES ACCORDING TO AGE

Clinical Features: The diagnosis of UTI was mostly based on the clinical presentation of the patient. Majority of the patients experienced symptomatic UTI (77.3%) followed by asymptomatic UTI (22.7%). Fever was the most presenting symptom in 152 (70.4%) patients. Other common symptoms include dysuria (37.5%), flank pain (17.1%), supra-pubic pain (13%), urgency (18.5%), altered sensorium 10 (4.6%), pain in perennial region (3.7%) and thrombocytopenia (2.3%). Most of them have upper UTI symptoms (fever and flank pain) than lower UTI symptoms (dysuria, urgency, frequency) **Fig. 2.**

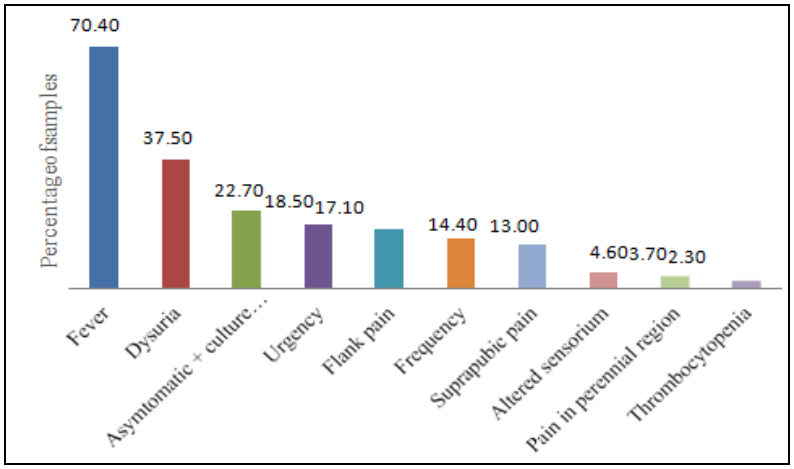

FIG. 2: DISTRIBUTION OF SAMPLES ACCORDING TO CLINICAL FEATURES

Causative Organism: UTI are caused by both gram-negative and gram-positive bacteria, as well as by certain fungi. The commonest causative organism was *E. coli* (51.9%), followed by *Klebisella pneumoniae* (30.1%), Pseudomonas (9.3%), Enterococcus (3.7%), Candida (2.8%) and Staphylococcus (2.3%).

TABLE 1: DISTRIBUTION OF SAMPLES ACCORDING TO ORGANISM IDENTIFIED

Organism	Frequency	Percentage
E. coli	112	51.9
Klebisella species	65	30.1
Staphylococcal	5	2.3
Enterococcus	8	3.7
Pseudomonas	21	9.6
Candida species	7	2.8

Antibiotic Utilization: In most cases antibiotics started empirically before culture report was obtained. Definitive therapy is based on information determined from the antimicrobial resistance.

Among empirical antibiotics Inj. Cefoperazone Sulbactum (51.4%) were most commonly prescribed followed by Tab. Ciprofloxacin (19.1%), Inj. Piperacillin Tazobactum (18.1).

Also Inj. Cefoperazone Sulbactum was commonly prescribed among definitive antibiotics.

TABLE 2: FREQUENCY AND PERCENTAGE DISTRIBUTION OF SAMPLES ACCORDING TO EMPIRICAL AND DEFINITIVE ANTIBIOTICS

Drug class	Antibiotics	Empirical		Definitive	
		Frequency	Percentage	Frequency	Percentage
		111	51.4	115	53.2
Cephalosporins + β-lactamase	Inj. Cefoperazone+Sulbactam				
Pencillin + β-lactamase	Inj. Piperacilin + Sulbactam	39	18.1	31	14.4
	T. Amoxicillin/Clavulanate	27	10.3	7	3.2
	Inj. Amoxicillin/Clavulanate	1	0.5	-	-
Fluoroquinolones	T. Ciprofloxacin	46	19.0	46	21.3
	Inj. Ciprofloxacin	2	0.9	1	0.5
	Inj. Levofloxacin	1	0.5	1	0.5
	Inj. Ofloxacin	9	4.2	-	-
Carbapenem	Inj. Meropenam	16	7.4	27	12.5
Cephalosporins	Inj. Ceftriaxone	4	1.9	2	0.9
Nitroimidazole	Inj. Metronidazole	4	1.9	-	-
Nitroimidazole	T. Metronidazole	3	1.4	-	-
Tetracycline	T. Doxycycline	9	4.2	2	0.9
Antifungal antibiotics	T. Fluconazole	-	-	3	1.4
	Inj. Fluconazole	-	-	3	1.4
Polymixins	Inj. Colistin	-	-	6	2.8
Macrolides	Inj. Azithromycin	1	0.5	-	-
Oxazolidinone	Inj. Linezolid	1	0.5	-	-

De-escalation of Antibiotics: The rate of successful de-escalation was 26.9% (58 patients), while 73.1% (158 patients) failed de-escalation **Fig. 3**.

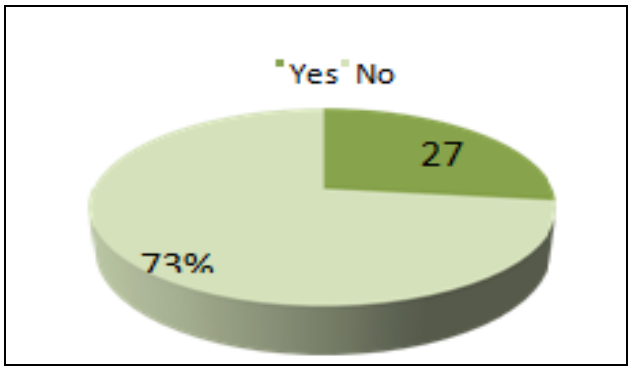

FIG. 3: DE-ESCALATION OF OF ANTIBIOTICS AS PER THE PROTOCOL

45 patients (20.6%) do not need antibiotic therapy because patients having asymptomatic bacteriuria does not benefit from treatment. The most commonly used drug in de-escalation was Inj. Cefoperazone Sulbactum. Most of the patients were sensitive to Tab. Nitrofurantoin (17.9%).

Impact of de-escalation on Length of Stay and Cost: Among the participants, 73.1% failed in de-escalating antibiotics, which resulted in an increased length of hospital stay depicted in **Fig. 3**. Duration of antibiotic prescribed and duration of antibiotic as per the protocol were analyzed. The association between the de-escalation of antibiotic and length of stay (LOS) were assessed. 69% (149) were prescribed for seven days. In the case of asymptomatic bacteriuria, treatment is unnecessary according to protocol. But in our study, symptomatic patients (22.7%) were prescribed different antibiotics.

TABLE 3: FREQUENCY AND PERCENTAGE DISTRIBUTION OF SAMPLES ACCORDING TO DURATION OF ANTIBIOTICS PRESCRIBED

Duration (in days)	Duration of choice of antibiotic prescribed		Duration of antibiotic as per the protocol		Difference in duration	
	Frequency	Percentage	Frequency	Percentage	χ^2 value	p value
0	-	-	45	20.8	36.091	0.001***
4	1	0.5	2	0.9		
5	54	25.0	58	26.9		
6	2	0.9	4	1.9		
7	149	69.0	105	48.6		
8	7	3.2	2	0.9		
9	3	1.4	-	-		

***p<0.001

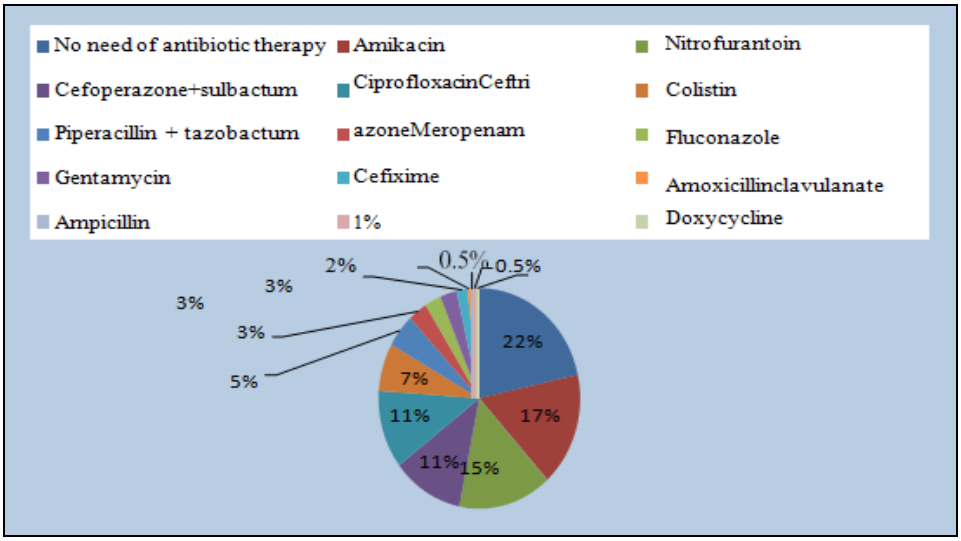

FIG. 4: IDEAL CHOICE OF ANTIBIOTICS AS PER THE PROTOCOL

The hospital LOS was significantly high in non-deescalated patients compared to succeed group. The *p-value* was <0.001 and showed a significant association between de-escalation and length of stay. The cost of the antibiotic prescribed and cost of antibiotic as per protocol were checked and calculated the cost difference. The difference in cost per day was further divided into five categories and evaluated for de-escalation's impact on the cost of prescribed antimicrobials.

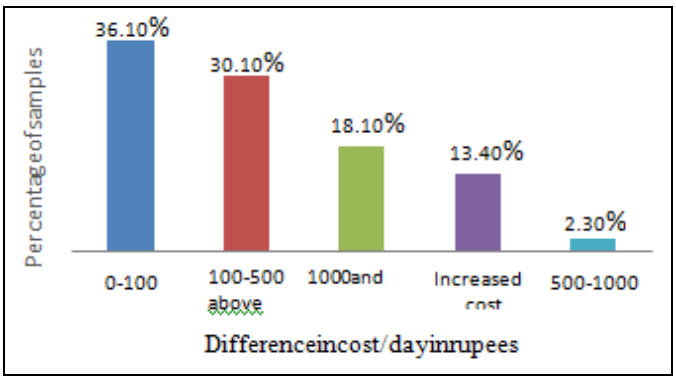

FIG. 5: DISTRIBUTION OF SAMPLES ACCORDING TO DIFFERENCE IN COST OF DRUGS/DAY

Most antibiotics were not prescribed according to protocol. Hence, there is a considerable difference in cost **Fig. 5,** which shows the impact of de-escalation on the cost of antibiotics prescribed. The mean cost of antibiotics prescribed was 752.45. As per the protocol, the mean cost was 329.31 **Fig. 5**. The *p-value* was <0.001 and shows a significant association between de-escalation failure and the cost difference of drugs/day.

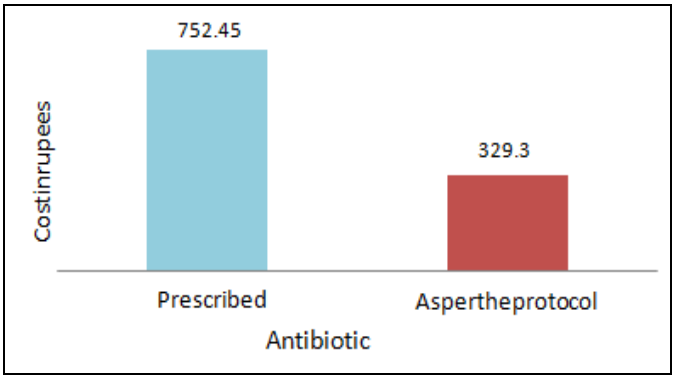

FIG. 6: MEAN COST OF ANTIBIOTICS PRESCRIBED AND AS PER PROTOCOL

Adverse Effects Associated with Antibiotic Usage: Among 218 patients, 97.7% does not experience any adverse effects. 1.8% had gastric irritation associated with antibiotic usage, and 0.5% experienced exanthem.

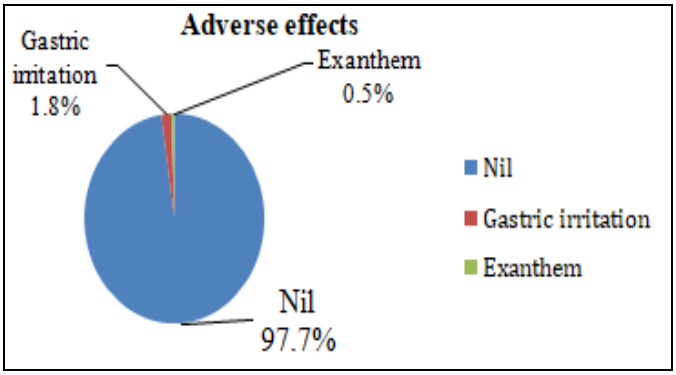

FIG. 7: DISTRIBUTION OF SAMPLES ACCORDING TO ADVERSE EFFECTS

DISCUSSION: This study showed that out of 114 patients, females were more likely to get UTI, comprising 77.1%, than males, which constitute only 28.9%. According to the National Institute of Diabetes and Kidney Diseases, women are more likely to develop UTIs because they have a shorter urethra than men. Similar observations were found in previous study [9].

Nearly 1 in 3 women will have had at least one episode of UTI requiring antimicrobial therapy by the age of 24. This study divided patients into four groups based on different ages. The highest incidence was seen in the age group of 36-45 years, while other studies reported more incidence in a higher age group [10, 11, 12]. UTI was diagnosed based on positive blood cultures, urine cultures, and a review of the medical records. Of these, the commonly isolated organism was *Escherichia coli* (27%) followed by *Klebsiella pneumonia* (12.4%), *Proteus mirabilis* (4.5%) which were similar to the findings of some other studies [11, 13, 14].

Other organisms identified were *Pseudomonas aeruginosa* (4.5%) *Enterococcus faecalis* (5.6%) and *Staphylococcus aureus* (5%). Cephalosporins were the most common antimicrobial group used in this study, similar to previous study results [15] whereas another study revealed amikacin as the most commonly used antimicrobial [16]. In the current study, the rate of successful de-escalation based on susceptibility response was 26.9% (58 patients) while 73.1% (158 patients) failed de-escalation. Empirical treatment with broad spectrum intravenous (IV) antibiotics can reduce the unnecessary risks and cost of disease progression associated with treatment failure. However, antibiotic de-escalation by switching from a broadspectrum empiric antibiotic therapy to narrow spectrum after obtaining microbiological data is recommended to prevent the emergence of resistant bacteria. De-escalation is safe and effective in most patients and in most infections. Few studies evaluated the impact of antibiotic de-escalation on patients admitted with UTIs [17]. Some studies on UTI patients with secondary bacteremia showed that antibiotic de-escalation was under-prescribed, although it was associated with decreased hospital mortality and hospital LOS [18, 19]. Several studies have demonstrated that antibiotic de-escalation is a safe and beneficial strategy [20, 21].

To optimize de-escalation rates, we should work to disseminate results from observational studies and expert opinions that suggest de-escalation is a safe and economical strategy which can benefit both patients and care institutions. These benefits include less pressure on microbial selection and reduced LOS and hospital costs.

Limitations: This study was conducted at a single center in one setting and excluded pediatric and psychiatric patients. The study describes the prescribing patterns and physician adherence to treatment guidelines in a single study setting and the results cannot be generalized. The study focused on inpatients in whom the infection is usually more severe than those treated on an outpatient basis. The study only considered drug utilization patterns over a 6 month period, which may differ from the pattern obtained over a longer period.

CONCLUSION: Antibiotic de-escalation is a vital antimicrobial stewardship plan. The findings of this study showed that de-escalation was associated with better patient outcomes in patients admitted due to UTIs (*i.e.*, reduced hospital LOS). Additional data are desirable on a large scale to assess causes for de-escalation failure. The role of clinical pharmacists is to ensure rational, effective, and safe treatment for the patient in their care. This involves interacting with patients to identify the

medicines they have been taking before they were admitted to the hospital and educating them on using their medicines when they leave the hospital. By their expertise and mission of ensuring optimal patient outcomes, pharmacists should work in the process of improving antibiotic use through de-escalation. The primary focus of de-escalation is to demonstrate long-term benefits through a positive impact on antibiotic resistance development. A significant secondary goal is financial savings through improved cost-effectiveness. With the onset of antibiotic resistance as a global threat, de-escalation of antibiotics is an area of paramount importance. This ensures the use of narrow-spectrum antibiotic agents, thus reducing the risk of antibiotic resistance development. It is also recommended that antibiotic management should, as much as possible, limits the pre-culture use of antibiotic agents with broad-spectrum antibacterial effects to a single starting dose or 24 h, depending on when microbiological results are available. This change of attitude toward antibiotic utilization can reduce the risk of selection of multi-drug resistant strains and decrease the cost of drug treatment, a significant proportion of which goes to antibiotic use.

ACKNOWLEDGEMENTS: The authors are grateful to the management and staff of Ezhuthachan College of Pharmaceutical Sciences and NIMS Medicity for their support.

CONFLICTS OF INTEREST: None

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How to cite this article:
Shareef A, Vasavan A, Roy A, James AJ, Nair CC and Aiswarya S: Antibiotic de-escalation in bacteremic uti & it's impact on cost and length of stay-a prospective observational study in a Tertiry Care Teaching Hospital in South Kerala. Int J Pharm Sci & Res 2023; 14(9): 4572-79. doi: 10.13040/IJPSR.0975-8232.14(9).4572-79.